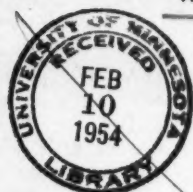


CLINICAL PROCEEDINGS

of the
CHILDREN'S HOSPITAL

WASHINGTON, D. C.



October 1953

VOLUME IX

NUMBER 10



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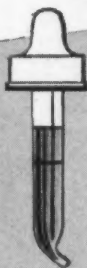
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CLINICAL PATHOLOGY

OF THE

INTERNAL ORGANS

AND

THE

SYSTEMS OF THE BODY

BY

JOHN H. HARRIS, M.D.

OF THE

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CHICAGO, ILL.

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HYPOPROTHROMBINEMIA

Case Report No. 274

Jean D. Lockhart, M.D.

INTRODUCTION

Hypoprothrombinemia, a not uncommon complication of many childhood diseases, represents a type of coagulation defect which usually may be corrected quickly, even before the underlying cause of the condition has been determined. The following report of a patient who was admitted to Children's Hospital recently,* illustrates the development and treatment of hypoprothrombinemia.

CASE PRESENTATION

K. P., a nine-month-old white male, was admitted on July 31, 1953 because of "bronchitis". One month prior to admission he had developed anorexia and irritability, and began to lose weight. Physical examination was negative. Five days prior to admission he had fever of 104.0 degrees, with cough and pyuria. This was treated with a three-day course of aureomycin. Temperature returned to normal for four days, and then fever recurred and the cough worsened. There was a total weight loss of two pounds in one month.

Past History

The patient was born in Austin, Texas, on October 22, 1953, weighing 6 pounds, 7 ounces. He was breast fed, and gained no weight in the first month. At the age of six weeks he had "influenza," and was treated with penicillin and aureomycin. Solid foods were not started until the child was five months of age, but were fairly well taken until the present illness, at which time (one month prior to admission) he refused all solids and even liquids except breast milk. He had been on Tri-vi-Sol since about one month of age. Bowel movements were said to have been normal.

A four-year-old brother was in good health except for hay fever. The patient's mother suffered intermittently from hay fever. Her dietary history was normal. Because she was an orphan the mother could give no family history. Paternal family history was non-contributory.

Rectal temperature on physical examination was 103 degrees; weight was 15 pounds. The child was underdeveloped and poorly nourished, pale, and irritable, without jaundice or cyanosis. A dry cough was present. There were some palpable anterior and posterior cervical nodes. The heart and lungs were normal; the liver was palpable two cm. below the costal margin, and the spleen could not be felt. Genitalia, extremities and skin appeared normal. The neurological examination was normal.

Complete blood count on admission revealed: Hemoglobin, 10.5 grams, hematocrit, 38 per cent; 12,700 white blood cells with 56 segmented cells, 7 band forms, 35 lymphocytes, and 5 monocytes. Urine culture upon admission yielded proteus vulgaris, sensitive to chloromycin and streptomycin.

The patient was treated with penicillin, streptomycin and clyses. He refused all

* On the service of Dr. Maynard Cohen

food except breast milk, and remained irritable. Two days after admission, he began to bleed from injection sites. The following day he had a bloody stool, and developed hematomas at sites of handling. Aureomycin was started and given for two days, following which the patient's temperature returned to normal, and the cough gradually improved, but the bleeding tendency persisted.

Laboratory investigation revealed the following: On August 3, 1953, the hemoglobin was 11.0 grams; hematocrit, 39; white blood cells were 15,600. Bleeding time was 2 minutes and the tourniquet test was negative. On August 4, the Lee-White clotting time was 13 minutes, the total protein was 6.4 grams (albumin, 4.8; globulin, 1.6). Prothrombin time, using the one-stage method, was reported as no clot present after 131 seconds.

In view of the hypoprothrombinemia, the patient was given 72 mgm. of vitamin K intravenously (Synkavite), and transfused with 50 cc. whole blood on August 4. Oral and intramuscular Vitamin K was also started. On August 5 the prothrombin time was 64 per cent of normal, and the child received another transfusion of 110 cc. of whole blood. On August 6, the complete blood count showed hemoglobin, 8.5 grams; hematocrit, 32; white blood cells, 11,500. Urinalysis that day showed the urine to be clear, alkaline, without sugar, acetone or albumin, with numerous white blood cells, 1-2 red blood cells, white blood cell clumps and cylindroids, and a few casts. On August 8, the thymol turbidity was 2.1 units, and the cephalin flocculation test results were negative in 24 and 48 hours.

Teleroentgenogram on August 1 showed "some interstitial infiltration in the left lung and increased vascularity on the right." Intravenous pyelogram on August 9 was normal, but the radiologist noted generalized demineralization of the bony structures.

Clinically, there was no evidence of bleeding after August 5, and the hematomas began to disappear. The child continued to be pale. He was discharged on August 9, with the final diagnosis of: tracheobronchitis, pyuria, and hypoprothrombinemia.

After discharge, the patient's appetite improved and he began to gain weight. It is noteworthy that this mother had persisted in nursing the infant beyond the usual time, despite recommendations to the contrary. The child was gradually weaned, however, did well, and there have been no recurrences of bleeding. About one month after the infant's discharge, he had an upper respiratory infection, along with the rest of the family, and because of his possible drug sensitivity received no treatment whatsoever. He recovered uneventfully.

DISCUSSION

All the known causes of hypoprothrombinemia may occur in infancy and childhood, and some are confined to the pediatric age group. They may occur singly or, as in the above patient, in combination. In this child, chronically poor diet, plus infection, presumably depleted the stored Vitamin K, and even the relatively short enteral administration of aureomycin reduced the coliform bacteria which would otherwise have manufactured the vitamin.

A general classification of etiologic factors in hypoprothrombinemia includes:

1. "Hemorrhagic diseases of the newborn".
2. Lack of Vitamin K in the diet (rare), or prolonged vomiting in infancy.

3. Poor absorption of Vitamin K in the intestinal tract, due to obstructive jaundice from any cause, biliary fistulae, sprue, pancreatic disease, intestinal obstruction, colitis, prolonged diarrhea, or excessive use of any cathartics.
4. Bowel sterilization, with suppression of coliform bacteria which synthesize Vitamin K.
5. Liver damage, causing failure of utilization of Vitamin K in the production of prothrombin.
6. Increased metabolism of Vitamin K, as in hyperpyrexia or hypervitaminosis A.
7. Drug-induced hypoprothrombinemia (dicumarol, salicylates, quinine, propylthiouracil, para-amino salicylic acid, and others).
8. Hereditary anomaly.
9. Idiopathic hypoprothrombinemia^(1,6).

Hemorrhagic Disease of the Newborn

The earliest manifestation of hypoprothrombinemia, so-called "hemorrhagic disease of the newborn", is still the most mysterious. To understand this, it is necessary to understand the two methods for measurement of prothrombin. In the one-stage method (Quick, 1935), calcium and thromboplastin are added in optimal amounts to the patient's oxalated plasma, and the clotting time of the mixture is recorded. In the two-stage method (Warner, Brinkhaus and Smith, 1936), thrombin is formed in a mixture of thromboplastin, calcium, and the patient's oxalated plasma containing an unknown amount of prothrombin. Samples are taken from this incubation mixture at intervals and added to samples of fibrinogen solution, the clotting times of which are recorded. The clotting times of the fibrinogen give a measure of the amount of thrombin present and when the maximum thrombin concentration is reached it is supposed that all of the prothrombin is converted and that the thrombin level at this point gives a measure of the amount of prothrombin present⁽¹⁾.

It has been repeatedly observed that the blood of the newborn baby has a prothrombin level of only about 30 per cent when measured by the two-stage method, and that this level remains low for many months. When measured by the one-stage method, on the other hand, the prothrombin level is low for a very limited period in the first ten days of life. The lengthened one-stage prothrombin time of infants is reduced by Vitamin K or K₁, and if the Vitamin K is given early the hypoprothrombinemia can be prevented⁽⁶⁾. Transfusion is surprisingly ineffective as a method of treatment.

The newborn baby has all of his prothrombin in the free state (which alone is measured by the prothrombin time), unlike the adult, in whom the

inactive form, prothrombinogen, constitutes about 75 percent of the total prothrombin. The baby is thus born without any appreciable supply of Vitamin K and no reserve of inactive prothrombin. Prothrombin is known to be promptly utilized or metabolized in the body, probably in the lungs⁽⁶⁾, most of it disappearing from the circulation in 24 hours if its formation by the liver is not maintained. A temporary lack of Vitamin K is therefore likely to cause a rapid and severe diminution of prothrombin^(9, 10).

The average pregnant woman shows progressive acceleration of prothrombin time (by the one-stage method) beyond the normal range through the course of pregnancy, and lasting through the first week post-partum⁽¹¹⁾. Nevertheless, before the introduction of Vitamin K a tendency to hemorrhage was seen in approximately 1 in every 400 newborn babies. The average time of onset in these cases was 41.5 hours after delivery and hemorrhage usually occurred before the fifth or sixth day. In one series the death rate was 8.2 percent⁽¹²⁾; in others, as high as 38 percent⁽¹³⁾.

Prematures and Vitamin K

The practice of administering Vitamin K routinely to newborns has thus developed, and since its institution few cases of hemorrhagic disease are seen. Because of the storage deficiencies of premature infants and their slightly lower prothrombin time as compared with their full-term counterparts, it is also common practice to give Vitamin K to prematures. This results in slightly higher prothrombin levels, but no less hemorrhagic manifestations⁽¹⁴⁾.

Hereditary Hypoprothrombinemia

In point of time, the next form of hypoprothrombinemia to manifest itself in the infant may be the congenital idiopathic type. Inherited factors may play a part in this disorder. Symptoms begin at one week to eight years, and the coagulation time may be prolonged, but the bleeding time is usually normal. This form of hypoprothrombinemia is *not* influenced by Vitamin K administration, even for a short time^(15, 16).

Miscellaneous Causes of Hypoprothrombinemia

In 1941, Grossman reported six cases of hypoprothrombinemic states from Children's Hospital, Washington, D. C., of which all but one were secondary to severe liver disease⁽⁴⁾. This is probably the most important single cause of the condition in pediatric practice. Children with biliary atresia have several causes for bleeding tendencies, of which hypoprothrombinemia is only one. In far advanced cases, where liver damage is severe, "labile factor", and prothrombin are depleted simultaneously, and at the time of death, prothrombin time estimations may be very prolonged,

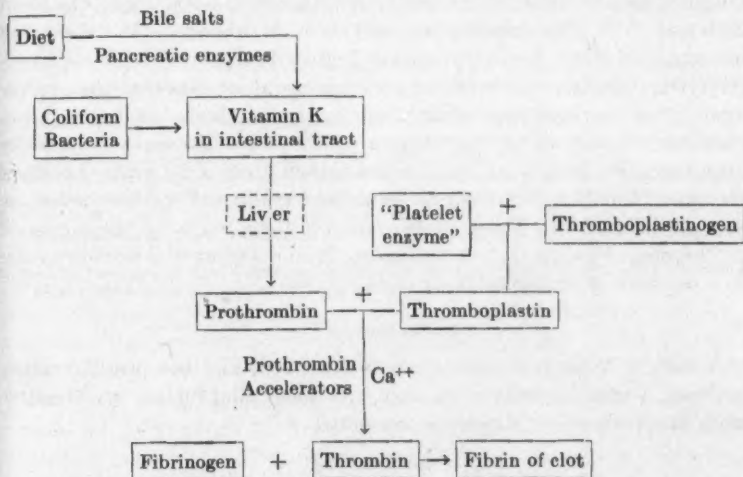
despite adequate Vitamin K supplements. (Fresh plasma is said to contain a "labile factor", since the one-stage prothrombin time of oxalated plasma lengthens on storage. The prothrombin time is restored to normal by fresh plasma adsorbed with $\text{Ca}_3(\text{PO}_4)_2$ ⁽¹¹⁾.)

Bowel sterilization, such as with streptomycin, may result in hypoprothrombinemia, for reasons already indicated⁽¹⁷⁾. Many other antibiotics are anticoagulants in vitro, when used in greater concentrations than can be obtained in vivo⁽¹⁸⁾.

Since Vitamin K is one of the fat-soluble vitamins, bile and pancreatic lipase are important for its absorption. Biliary and pancreatic disorders are well recognized causes of low prothrombin states. Hypoprothrombinemia may also be produced by drugs such as dicumarol, salicylates, quinine, propylthiouracil, tromexan, and phenylinandione, by virtue of a direct anti-prothrombin effect. Para-amino-salicylic acid, a common adjunct in the treatment of pulmonary tuberculosis, may exert a toxic effect on the liver with resultant hypoprothrombinemia.

Prothrombin Accelerators

There have been recent reports, simultaneously from several different laboratories, concerning a substance that is concerned with the speed of formation of thrombin from prothrombin. In 1947, Owren in Norway named "factor V" a substance whose presence in the plasma is necessary for rapid and complete thrombin formation. In Australia, investigators



Role of Prothrombin in the Clotting Mechanism

found a "prothrombin accelerator substance" in plasma, which may be identical with factor V. A factor in *serum* which accelerates the conversion of prothrombin to thrombin has been described as S.P.C.A. (Special prothrombin conversion accelerator), and cases of congenital S.P.C.A. deficiency have been described^(19, 20). This may be the substance which Owren designates "Factor VI"⁽²¹⁾ or Seegers' "Serum Ac-Globulin"⁽²²⁾. There is still a certain amount of confusion surrounding these prothrombin accelerators, part of which may be due to nomenclature. It is becoming apparent, however, that the serum prothrombin accelerators are the active substance, while the plasma prothrombin accelerators are relatively inert, and may be considered as having to react with thrombin in order to produce the serum accelerators. The classic concept of the clotting mechanism is undergoing constant revision, as experimental work becomes more exact and more complicated. It has been said, for example, that the blood of the newborn infants has never been examined by modern methods. (Biggs).

Treatment

The blood level of prothrombin must decline to about 10 or 15 percent of normal before hemorrhages occur⁽²³⁾. At that time, the hypoprothrombinemia constitutes a medical emergency, and therapy should be instituted without delay. Experimental work on Dicumarol-induced hypoprothrombinemia originally indicated that the intravenous administration of 64 mgs. of menadione sodium bisulfite (2-methyl-3-phytyl-1,4-naphthoquinone) usually returned the prothrombin times to normal levels in about 24 hours^(24, 25). The response was said to be in proportion to the amount of compound given. Further studies indicated that vitamin K₁ (2-methyl-3-phytyl-1,4-naphthoquinone) and its oxide are more effective than menadione or synkavite (tetrasodium 2-methyl-1,4-naphthohydroquinone phosphoric acid ester) in counteracting a prothrombin deficiency induced by Dicumarol. Vitamin K₁ given intravenously in doses of 10 mgm./kg. raises the prothrombin level within an hour, and maintains effective levels for over 48 hours^(26, 27). These studies are valid inasmuch as the increased prothrombin time in both avitaminosis K and Dicumarol toxicity is due to a decrease of prothrombin.

SUMMARY

A case of hypoprothrombinemia is described, and the possible causes outlined. Various aspects of etiology, treatment, and further investigative work on prothrombin deficiency are noted.

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DIAGNOSIS AND MANAGEMENT OF TRAUMATIC PANCREATITIS

Gerald H. McAteer, M.D.

Bennett Creech, M.D.

INTRODUCTION

In most hospitals surgeons are frequently called to the emergency room to see patients who are the victims of trauma. The trauma may be due to many different circumstances, such as automobile accidents, industrial accidents, falls down steps or from buildings, falls from bicycles, and injuries incurred during sports activities.

In many instances the injuries are multiple, involving head trauma, crushing injuries of the chest, fractures of the spine or pelvis and traumatic damage of varying degree to the extremities. The abdomen should never be forgotten as a site of serious injury, for a ruptured liver, spleen, or kidney, or a perforation of the intestine demands emergency surgery as a life-saving measure.

The abdominal organ which is most likely to be overlooked in these cases is probably the pancreas, since injury to it is not readily apparent. Due to its deep position and good protection, injury to the pancreas is relatively uncommon, and there are very few surgeons who have extensive experience in dealing with it.

Traumatic pancreatitis is often associated with injuries to important adjacent viscera, but it may occur alone, without injury to other structures.

Injuries of the pancreas are usually classified as: (1) *penetrating*, in which trauma is produced by missiles, blades, or other instruments of direct force used most often in warfare; and (2) *non-penetrating* or *crushing* injuries, in which sudden blunt violence, direct or indirect, to the upper abdomen, forcibly wedges the pancreas against the body of the first lumbar vertebra. This is the type seen in civilian life, and it is this type of isolated traumatic pancreatitis with which this paper is concerned.

PATHOLOGY

The immediate effect of crush injury is a traumatic pancreatitis, the severity of which depends upon the extent of the original injury. The pancreas may be crushed, ruptured, or torn across. There is more likelihood of a severe injury if the trauma is very sudden and produces its effects before the abdominal musculature has time to guard against the blow. In such circumstances as these the pancreas alone may be injured⁽²⁾. The injury may vary from simple bruising of the gland to complete rupture, and the condition of the patient will vary accordingly. As most of these injuries are relatively mild, transient edema may be the only pathologic finding. If

bruising is more severe, immediate or late hemorrhage may occur. This hemorrhage may or may not be confined beneath the capsule of the gland.

A dangerous situation may therefore arise if there is extensive hemorrhage; if activated pancreatic enzymes escape into the surrounding tissues; or when the duct of Wirsung is torn, causing diversion of the pancreatic juice from the gastrointestinal tract. As a result of the latter injury, widespread necrosis, a pancreatic cyst, or a persistent external fistula may develop. This may be followed by recurrent attacks of pancreatitis or recurrent pancreatic fistula.

EXPERIMENTAL STUDIES

Popper, studying injuries of the pancreatic duct in 1949, found that transection or lengthwise incision of the main pancreatic duct in dogs without ligation of the open ducts was *not* followed by any acute intraperitoneal process. When the dogs were starved before and after surgery, the opening in the pancreatic duct was sealed by omentum or a loop of bowel. In animals which were fed preoperatively or postoperatively, or which were given cholinergic drugs, intra-abdominal fat necrosis occurred. This seemed to indicate that a protective mechanism consisting of plugging of the open duct by omentum, together with inhibition of pancreatic secretion, prevented intra-abdominal spilling of pancreatic juice⁽²⁾. This investigator later studied the effects of extensive crushing and tearing of the pancreas and he found that these injuries were relatively well-tolerated by the dog and were not followed by acute intraperitoneal processes, whether the animals were fed or starved before and after surgery. Acute fat necrosis did not occur in these experiments probably because the glandular tissue of the pancreas was so severely damaged that external pancreatic secretion was drastically depressed.

These experiments indicate that the pancreas in the dog is not an excessively delicate organ but is rather resistant to injury. This is, of course, in sharp contrast to the generally accepted characteristics of the pancreas of man. These findings raise the question as to whether the pancreas of man actually differs from that of the dog in its resistance to injury and whether the assumption of extreme vulnerability of this gland in the human is not based on observations which may be superseded by our present knowledge and modern surgical technique⁽³⁾.

Popper and Necheles⁽⁴⁾ extended the scope of these experiments and, in addition to the previous experimental findings, demonstrated that the presence of a moderate amount of blood or bile in the peritoneal cavity did not alter the uneventful course following trauma to the pancreas. Applying the knowledge gained experimentally, they postulated that following severe injury or major surgery on the pancreas a drastic inhibition of pancreatic

secretion will occur which will resist stimulation by potent stimuli and will permit an efficient sealing of the pancreatic wound. They felt that the protective phenomena demonstrated in their experiments may explain why extensive surgical procedures on the pancreas are tolerated relatively well, while relatively insignificant surgical or accidental injuries are followed not infrequently by extensive intra-abdominal fat necrosis.

CLINICAL PICTURE

Most injuries to the pancreas are mild and consequently, in most cases, symptoms are rather vague, and not dramatic. The trauma which gives rise to traumatic pancreatitis may be surprisingly slight and is often not sufficient to produce any bruising or wounding of the abdominal wall. Symptoms may not appear for hours or even for days following the injury. One consistent finding is upper abdominal mid-epigastric pain. This pain may vary in severity and may or may not radiate to the back or to the flanks; Rini⁽¹⁾ found no such radiation in his cases. Nausea and vomiting are the rule. When more severe injury occurs, symptoms of shock may supervene and pain may be extremely severe.

With minimal injury, the findings upon physical examination may consist of only tenderness and some spasm in the right upper quadrant or the epigastrium; in some cases a tender mass may be palpable in this region. Peristalsis is usually diminished and there may be variable degrees of paralytic ileus with signs of slight to moderate distention of the abdomen. In severe pancreatic injuries with major pancreatic disruption, severe shock may be seen with irregular mottling of the skin, especially over the upper abdomen, and Grey Turner's sign may be observed in addition to the other findings. In extremely severe cases there may be marked cyanosis and dyspnea.

As in other patients with acute abdominal disease, laboratory findings are purely confirmatory. There is usually a rather marked leukocytosis with a great increase in young polymorphonuclear leukocytes. Serum and urinary amylase levels are elevated.

DIAGNOSIS

Conservative management of pancreatitis, regardless of type, produces the best results. Therefore, accurate diagnosis is important in these cases. Of course, penetrating wounds which cause massive intra-abdominal hemorrhage or ruptured hollow viscera, as manifested by a pneumoperitoneum, or severe crushing injuries which produce the same effects require emergency surgery.

When traumatic pancreatitis is associated with multiple injuries to the other abdominal viscera, the diagnosis is somewhat difficult. Symptoms

initiated by blunt trauma to the upper abdomen, delayed onset of symptoms, and progressive signs of irritation to the upper abdomen with lack of evidence of blood loss or pneumoperitoneum are extremely suggestive of traumatic pancreatitis. The presence of a gradually expanding mass in the epigastrium or in the flank following an upper abdominal injury should suggest the possibility of pancreatic injury. Such a mass may represent a hemotoma, a pancreatic cyst, or a pancreatic abscess. The sudden onset of shock in the absence of massive intra-abdominal hemorrhage should also lead one to expect trauma pancreatitis. Injuries of the pancreas which produce effusions and to the lesser omental sac usually produce pain in the left shoulder. Keight and Wright have advocated examining the fluid obtained by tapping for amylase as an aid in the diagnosis of acute conditions of the pancreas. In trauma especially, it may help to rule in or out intra-peritoneal hemorrhage or a ruptured intestine by disclosing blood or bile-tinged fluid⁽¹⁾.

COMPLICATIONS

The complications of traumatic pancreatitis are: (1) Acute pancreatic edema and pancreatic necrosis, (2) immediate or delayed massive hemorrhage, (3) pancreatic pseudocyst, (4) pancreatic abscess, (5) diabetes mellitus, (6) steatorrhea, (7) internal or external pancreatic fistulae, (8) sub-diaphragmatic abscess, and (9) pancreatic calcification⁽²⁾. The most important of these are pseudocysts, fistulae and diabetes mellitus.

Pancreatic pseudocysts following inflammatory conditions of the pancreas are much commoner in women, and are frequently associated with chronic cholecystitis and cholelithiasis; those resulting from trauma occur more commonly in males in association with greater hazards of their occupations.

A cyst may occur within a few days following an injury or even as long as a year later. Most will develop in four to six weeks. A cyst develops when bruising of the pancreas produces a hematoma beneath the capsule. The damaged pancreatic cells release their ferments into the hematoma and fat necrosis may occur. Trypsin from the damaged gland is activated by contact with the damaged and devitalized tissue, digesting the clot and giving rise to further bleeding from pancreatic vessels. This process may be repeated time and again so that a cyst is eventually produced. The cyst may become very large if the pancreatic duct is involved and pancreatic juice is added to the contents. The critical period for recurrence of hemorrhage into a cyst is from 10 to 14 days after injury. When hemorrhage occurs, it frequently causes severe epigastric pain and vomiting, associated with varying degrees of shock. These symptoms should lead the surgeon to suspect the onset of a pancreatic pseudo-cyst. On physical examination, such patients usually show a characteristic swelling

in the left hypochondrium. Roentgenographic study with the use of barium may reveal a large extragastric mass.

Pancreatic fistulae are extremely rare but these may occasionally develop following injury to a pancreatic duct or following drainage of a pseudo-cyst. In some cases of traumatic pancreatitis, fibrosis and even calcification of the pancreas may be the ultimate result and with extensive damage to the gland, diabetes mellitus may develop. Barnbrook⁽⁶⁾ reported a case of traumatic pancreatitis in a seven-year-old white male who developed acute diabetes mellitus on the eighth day following injury. Fortunately, this was a transitory diabetes and with standard medical treatment the patient became well. Six months later there was no evidence of diabetes.

TREATMENT

Treatment of this condition should be conservative. Uncomplicated cases are best treated by splanchnic nerve blocks for pain relief, intragastric suction with nothing by mouth, and the judicious use of parenteral fluids and drugs such as Banthine, to reduce the external pancreatic secretion. The carbohydrate metabolism should be carefully observed in order to anticipate the development of diabetes mellitus. For many years it has been advised that avoidance of stimulation of the external pancreatic secretion by food or medication be enforced. According to the experimental work of Popper and Necheles this is not nearly so important in severe pancreatic injuries as it is after minor injuries. The work of these investigators is encouraging, for in the seriously ill patient the complete avoidance of pancreatic stimulation may be a very difficult problem. In less severe injuries of the pancreas, however, stimulation of the secretions should be strictly avoided.

If the pancreas has been badly torn or lacerated, laparotomy will be necessary in order to repair the damage as much as possible and inspect adjoining viscera. Immediate operative management, however, is usually limited to evacuation of hematoma, control of hemorrhage, and adequate draining of the area. Attempts to suture a fractured gland are sometimes feasible. In severe injury with complete rupture there will be no doubt in the mind of the surgeon that laparotomy is required, although in many instances no exact pre-operative diagnosis can be made. In other cases it is also impossible to exclude the possibility of damage to the other intra-abdominal organs; in these cases laparotomy is indicated.

There are three satisfactory forms of treatment for pancreatic pseudocysts: (1) excision, (2) marsupialization and drainage, and (3) primary anastomosis between the cyst and the stomach or small intestine. The second method has been most widely used, but the third method will probably prove to be the best means of treatment⁽⁷⁾.

Approximately 80 per cent of pancreatic fistulae will close spontaneously, although some of them may drain as long as a year. A few of these may require surgical implantation of the fistulous tract into the stomach or intestine⁽⁷⁾.

CASE PRESENTATION

First Admission

G. A., a nine-year-old white male, was admitted to The Children's Hospital on June 28, 1953, with a history of having fallen from a bicycle three days prior to admission. The parents stated that they thought the handle bars struck the child in the upper abdomen as he fell. His local physician reported that the child had severe pain with tenderness over the entire abdomen following the injury. The tenderness persisted and localized over the right upper quadrant. During the three days prior to admission to the hospital the child's condition remained fairly good except for dehydration. He had considerable anorexia and would not take liquids well. Blood studies done by his local physician showed a leukocytosis of 14,100 with 87 per cent polymorphonuclears on one occasion and 13,600 leukocytes with 89 per cent neutrophils on a second occasion. The past history revealed no previous injury, operation, or allergy, and no serious illness except for two or three bouts of pneumonia.

Physical examination revealed a well-developed and well-nourished but rather thin and dehydrated white male in some acute distress from abdominal pain. The tongue was dry and coated and the breath was rather foul. There was some tenderness in the right lower chest. Examination of the abdomen revealed exquisite tenderness in the right upper quadrant and the presence of a tender mass which was thought to be continuous with the liver; this extended 3 centimeters below the costal margin. Peristalsis was diminished but there was no distention. Another observer on examination felt that the tender mass was separate from the liver. Rectal examination was negative. No other positive findings were elicited. The impression was that there was possibly a rupture of the liver or an early liver abscess.

Laboratory findings on admission revealed a hemoglobin of 13 grams with a microhematocrit of 44 per cent and 24,400 leukocytes with 89 segmented cells, 2 band forms, 8 lymphocytes and 1 monocyte. The urine was essentially negative except for the presence of 3+ acetone and was positive for diacetic acid. The CO₂ combining power was 37 volumes per cent. Roentgenograms of the abdomen in the upright and supine positions showed the liver to be somewhat enlarged. The child was examined later in the day and it was noted that the mass in the right upper quadrant was increasing in size. At that time the diagnoses which were suggested were liver abscess, subphrenic abscess, or ruptured duodenum.

On the day of operation, plasma chlorides were 124 meq/liter, the CO₂ combining power was 52 volumes per cent, and the microhematocrit was 38 per cent. Since injury to the liver could not be definitely excluded and the patient was not improving, exploratory laparotomy was performed on the day following admission. At laparotomy the pancreas was found to be enlarged, edematous, and hemorrhagic. The liver, spleen and kidneys were normal and there was no evidence of damage to hollow viscera. Drains were placed in the foramen of Winslow and the abdomen was closed.

Postoperatively, the child received nothing by mouth, but continuous Wangensteen suction by the use of a Levin tube was instituted. Nutrition was maintained by the use of intravenous fluids. On the third postoperative day peristalsis was normal, the tube being then removed. The patient took fluids well and gradually progressed to a

regular diet. On the third postoperative day the plasma chlorides were 99.5 milliequivalents per liter, the plasma potassium was 4.17 milliequivalents per liter, and the plasma sodium was 137.1 milliequivalents per liter.

The child seemed to make a very satisfactory recovery and was discharged to the care of his family physician.

Second Admission

One week after the child was discharged from the hospital he was readmitted with a history of some mild abdominal pain at home. He began to have severe intermittent abdominal pain about 24 hours before admission. This was associated with nausea and vomiting and intense backache. There was no shoulder pain. Physical examination revealed no jaundice and was negative except for some tenderness in the right upper quadrant and hypoactive peristalsis. The impression was that this was recurrent pancreatitis, possibly with biliary colic.

Laboratory findings on admission showed a hemoglobin of 12.7 grams per cent, a microhematocrit of 41 per cent, 18,800 leukocytes with 73 segmented cells, 8 bands, 15 lymphocytes, 1 monocyte, 3 eosinophiles and 1 basophile. The urine was negative except for the presence of 1+ acetone. Serum bilirubin was 0.2 mgms. per cent, the serum amylase was 75 mgms. per 100 ml. Roentgenograms of the abdomen in the erect and recumbent positions showed slight distention of the colon, several loops of small bowel and the stomach. The pattern was that of reflex ileus. The child again received nothing by mouth and Wangenstein suction was instituted. Intravenous fluids were given to maintain his fluid and electrolyte balance and he was given prophylactic doses of dicrysticin. The patient steadily improved and three days after admission the tube was removed and he resumed his usual diet without difficulty. He was discharged from the hospital on July 27, 1953, in good condition.

COMMENT

The cause of this patient's disability was traumatic pancreatitis, the correct diagnosis not being suspected before operation. It would seem that this patient is a good candidate to develop a pancreatic cyst in the future.

SUMMARY

1. A general review of the pathology, clinical picture, diagnostic features, complications and treatment of traumatic pancreatitis is presented.
2. Experimental studies of this condition are described.
3. A case of traumatic pancreatitis in a nine-year-old boy is reported.

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CONGENITAL ECTODERMAL DEFECT OF ANHIDROTIC TYPE
IN AN INFANT

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INTRODUCTION

Many cases with absence of the sweat glands have been reported in the literature. Most of these are variations of the syndrome, "Ectodermal Dysplasia of the Anhidrotic Type," which Matson and Williams⁽¹⁾ define as follows:

1. Heat intolerance due to generalized absence of sweat glands.
2. Partial to complete absence of both deciduous and permanent teeth with deformity of those which are present.
3. A decreased number of hair follicles and sebaceous glands as evidenced by a dry, smooth, shining skin and papillary lesions on face (degenerating sebaceous glands with surrounding acanthosis); absent or sparse, fine dry hair.

Other disturbances which are more or less commonly found in these patients are:

- Atrophic rhinitis,
- Chronic pharyngitis and laryngitis,
- Absent taste and smell,
- Deformed ears, such as satyr shaped, or absent lobules,
- Conjunctivitis,
- Absent tears,
- Apparent saddling of nasal dorsum,
- Absent mammary glands,
- Adrenal insufficiency,
- Everted lips with poor definition of the vermillion borders,
- Thickened cranial bones.

This syndrome has been described in only two negroes^(1, 4) in this country. Both of these had mixed ancestry. Many cases have been reported in Hindu families^(2, 3) and a few cases from Ceylon⁽³⁾ have been described.

An hereditary background with transmission of a recessive factor by a female to a male offspring has become widely accepted⁽¹⁾.

The following case presents many features of this syndrome.

CASE PRESENTATION

This negro male was admitted to the medical ward of The Children's Hospital when approximately three months of age on July 18, 1953, with a one week history of gradually increasing cough and a two day history of vomiting. No fever had been noted.

Past history, mother's pregnancy and a review of systems were essentially negative. Family history was negative with the exception of frequent brief contacts between patient and maternal grandmother who was recently discovered to have active pulmonary tuberculosis.

Physical examination on admission revealed the following pertinent findings: temperature 100.8°, moderate irritability, appearance of acute distress, fine hair, scaly eczematoid rash on face, dry skin, with small scattered cervical nodes.

Shortly after admission the patient had a yellow watery stool and was transferred to the Diarrhea Ward. Intravenous fluids and oral chloromycetin palmitate were begun. The following morning, the patient had improved and was placed on oral feedings of Hi-Pro 1:3, tea and water.

That afternoon, his temperature began rising. It was 103.4° at 4 p.m. and despite aspirin rose to 109.4° at 6 p.m. This latter temperature was rechecked by several other thermometers in the presence of two nurses and two resident physicians. The patient was alert and responsive and did not appear in any distress. His skin was dry and shiny. No perspiration was noted. Aspirin, alcohol sponging and cool water enemas brought temperature down to 103.0°. No perspiration was noted at this time either. The temperature remained at 103° for 12 hours despite aspirin and alcohol sponges, and then became normal.

Chest X-ray revealed questionable bronchiolitis. The chest was hyper-resonant to percussion and breath sounds were clear. Blood culture, febrile agglutinations, sickle cell preparation, rectal culture, and urinalysis were negative. The hemoglobin was 11.4 gms. and the white blood cell count was 9,000 with a slight shift to the left. The CO₂ combining power was 29 volumes per cent, PPD #1 was negative.

The diarrhea subsided in 2 days; the patient ate well and hydration became good.

Temperature spiked to 102.4° the following day, became normal and then rose to 103.2° the day after that. Throughout the remainder of patient's hospitalization, temperature spikes of 101° to 103° occurred at least twice weekly without apparent cause, except for one brief episode of purulent otitis media which responded to penicillin and sulfadiazine.

On the nineteenth hospital day, a subdural tap revealed 4 to 5 cc. of cloudy, xanthochromic fluid from the right side. This contained 320 mgm./100 ml. protein, 41 cells of which 28 per cent were red blood cells and 72 per cent were polymorphonuclear leukocytes. Four subsequent subdural taps were dry. A subsequent lumbar puncture was also negative. An electroencephalogram was negative. The neurological consultant stated that the eye grounds were normal and suggested a diagnosis of sinus thrombosis secondary to dehydration.

Skull x-rays were negative but did not allow good visualization of the mandible. No dental elements were definitely seen in the maxilla. The roentgenologist suggested the diagnosis of ectodermal dysplasia and requested further films of the mandible and the long bones. Repeat x-rays revealed definite evidence of tooth buds and the long bones were normal. Despite this, it was decided to investigate further the possibility of an ectodermal defect. Further review of family history then revealed the following pertinent findings:

1. Mother has had frequent episodes of malaise with fever during the summer. Perspiration occurred only in the axillae until she was placed on an increased salt intake. Perspiration now occurs over the entire body surface.

2. The mother has several irregularly spaced, peg-shaped teeth. Breasts and hair are within normal limits.

3. The father and two female siblings perspire freely. One sibling also has several irregularly spaced, peg-shaped teeth.

4. The maternal great-great grandfather was the only known Caucasian in the entire family tree. The patient's mother has no information regarding his state of health except that he lived to be 83 years old.

A perspiration test⁽¹⁾ using Minor's solution (Iodine 4 gm, castor oil 20 cc. and absolute alcohol 180 cc.) and corn starch was carried out with a 75 watt bulb in a floor lamp 12 inches from chest as a source of heat. A control patient (similar age and weight, post-diarrheal) was also used. The forehead, axilla, chest and groin were painted with the solution and dusted with corn starch. The corn starch and iodine react with the perspiration to produce a blue color. The results are as follows:

	Patient (Degrees F.)	Control (Degrees F.)
Base	98.4	99.0
Heat applied		
3 min.	No color change	Blue specks in all areas
5 min.	No perspiration noted	Areas completely discolored. Perspiration visualized grossly
10 min.	99.2 No perspiration noted	99.0
20 min.	99.4 No perspiration noted	99.0
40 min.	100.4 2 blue flecks in right axilla	98.8
Heat stopped		
60 min.	101.2	
80 min.	101.2	
140 min.	99.2	

Specimens of skin from right axilla and interscapular region were obtained by biopsy. Sweat and sebaceous glands in the deeper layers of the skin were noted in the axillary specimen. The other specimens revealed complete absence of sweat and sebaceous glands. The pathologist's diagnosis was congenital ectodermal defect.

Ear, eye, nose and throat consultation described atrophic rhinitis and a cup-shaped right ear.

Other pertinent physical findings were:

Hair: Fine and sparse on scalp, 1 to 3 cm. long. Eyebrows are fine and quite short, as are the eyelashes.

Lips: Large and everted. Vermillion boarder of lower lip is poorly defined but well defined on upper lip. Vermillion border is surrounded by a 1-2 mm. area of darkened brown pigmentation.

Skin: Uniformly dry, even in the body creases. The scalp appears thin and shiny with some scaliness.

Nails: Apparently well-formed finger- and toenails.

Breasts: Normal.

Lacrimation: Normal for age.

Further chest x-rays, PPD Intermediate, urinalyses, urine cultures, sickle cell preparations, and complete blood counts were negative. Blood cholesterol was 110 mgm per 100 ml. (normal infant 80-125 mgm per 100 ml.⁽²⁾).

The U. S. Weather Bureau reported a maximum temperature of 98° occurring at 4:30 p.m. on July 18, the day that this patient's temperature rose to 109.4°. At 6:00 p.m. when this elevation was recorded, the Weather Bureau reported a temperature of 95° and a humidity of 37 per cent. The patient's bed was located in the hottest part of the ward.

The consulting dermatologist concurred in the diagnosis of ectodermal defect based on absence of sweat glands. The possible diagnosis of ectodermal dysplasia

was deferred to a later date in order to follow hair growth and tooth eruption and structure.

The patient was discharged on August 28, to be followed in the Dermatology Clinic. The mother was instructed concerning the necessity of checking the temperature frequently, especially during hot weather and using cool water or alcohol sponges as indicated. She was cautioned to use aspirin only if the temperature did not fall after sponging.

Follow-Up: Up to the age of 5½ months, the patient has developed normally. No teeth have erupted yet and the scalp hair is still sparse. The patient has spiked temperature elevations frequently to 101° or 103° in hot weather. This was controlled by cool water sponging. The patient will be followed further.

DISCUSSION

Naomi Kanof M.D.:

This patient is unique from several points of view: the extraordinary temperature elevation, the almost complete absence of sweat glands, the age of the patient (4 months) and the absence of any other remarkable signs of ectodermal defection. It may well be that other ectodermal defects will become apparent as the child grows older. It is noteworthy, however, that the patient's finger- and toenails are of remarkably good consistency. Tooth buds are evident on X-ray and the skeletal structure appears to be normal. The question of the quantity and quality of the hair of the scalp, brows and eyelids may only be resolved later on. At the present time, were there no question of the presence of an ectodermal defect, the distribution and quality of the hair in these areas would not be considered remarkable. In the absence of other signs of ectodermal defect, this unique absence of only the sweat glands in the ectodermal structure is most bizarre, and it seems unlikely that this defection will be unaccompanied by others.

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ERYTHROBLASTOSIS FETALIS

(Sunday Conference)

M. B. W.*, a colored female, was admitted to The Children's Hospital on April 7, 1953 at 8 days of age because of increasing pallor.

The patient was born on March 30, 1953 at another hospital, following an uneventful pregnancy and delivery. At the time of discharge from the maternity hospital three days after birth, the mother thought the baby looked pale. The pallor progressed and on the evening prior to admission to Children's Hospital, dyspnea developed.

The baby's family includes three older siblings in good health who had no jaundice or anemia during their infancy. The parents were in good health. The mother was Rh negative and the father was Rh positive. The three siblings were all Rh positive. No antibody titers were done on the mother during her pregnancy.

The physical examination revealed a pale, moderately icteric 8-day-old colored female with a grunting respiratory rate of 40 per minute. There was a grade 2 to 4 blowing systolic murmur that was loudest along the left sternal border. The apex beat was not definitely left of the mid-clavicular line. The spleen was palpable 3 centimeters below the left costal margin and the liver was a similar distance below the right costal margin. There were no abnormal neurological signs.

The blood count at the time of admission disclosed 3.5 grams of hemoglobin with 540,000 red blood cells per cubic millimeter; there were 4 normoblasts and 2 erythroblasts per 100 white blood cells on the peripheral smear. The baby's blood type was "O", Rh positive. The Coombs test was strongly positive.

On the day of admission 100 ml. of type "O" Rh negative packed cells were administered. The hemoglobin on the following day was 9.5 grams per 100 ml. of blood. A 50 ml. transfusion of a similar type was given on the second hospital day. By the third hospital day, no jaundice was evident. The hemoglobin value on April 10, 1953 was 12.5 grams with a hematocrit of 37 per cent.

The patient was discharged on April 22, 1953 to be followed in the blood dyscrasia clinic. The patient's condition at the time of discharge was excellent.

DISCUSSION

Dr. Ramaekers†:

I think the best way to discuss this case would be to consider the subject generally and to discuss first very briefly, the basic principles of the pathogenesis of the disease, erythroblastosis fetalis. As you all know, the disease is the result of an active immunization of the mother by an antigen present in the fetal red cells. This antigen usually is the so-called "Rh factor", which the fetus has inherited from his father. There exist, however, a number of other blood group factors, each with a different antigenic power, which are able to immunize a mother. The mother produces antibodies against these antigens. A certain variety of these antibodies, the so-called incomplete antibodies are able to pass the placental barrier

* This patient was on the service of Dr. Preston McLendon.

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and combine with the fetal red cell, as a result of which the normal life time of the red cell is shortened; there is an increased hemolysis. It is important to keep this increased hemolysis in mind, since it is the central pathophysiological principle in erythroblastosis. The disease starts in utero from the moment that the antibody crosses the placenta and combines with the antigen. Most of the symptoms of the disease, if not all, are the result of a hemolytic anemia, beginning in utero and continuing after birth as long as there remain antibodies in the infant's circulation.

The condition of affected babies at the moment of birth is extremely different and the clinical picture at birth is very variable. On the one side we see a dying or stillborn infant and on the other side we find a baby who does not show any signs or symptoms of the disease. The height of the mother's antibody-titer certainly cannot fully explain this variability, although there is a very close correlation between those titers and the severity of the disease. Other factors which have an influence on the course of the disease in utero is the length of time the fetus is subjected to the antibodies and the efficiency of the compensatory mechanism of the fetal hemopoietic tissue to counteract the increased hemolysis, by a high red cell output. The avidity of the antigen to combine with the antibody is another possibly important factor which determines the severity of the disease. The idea that the fetal or maternal adrenal function has anything to do with the great variability seems only fashionable and finds no support in clinical or laboratory investigations. We do not understand why in certain cases the lifetime of the sensitized fetal cell is normal, while in others it is only very short. We do not know the answer to the great variability of the disease.

The clinical diagnosis at birth is not too difficult, especially if clinical signs are present. On the basis of antibody studies made on the mother during pregnancy, the physician is able to diagnose hemolytic disease in the infant. Among the clinical symptoms mentioned in textbooks, jaundice is almost always mentioned as an important characteristic of erythroblastosis. Our experience is different. There is no visible jaundice at birth, not even in the most severe hydropic baby. Quite often, however, there is a yellow pigmentation of the cord and the vernix. As further evidence of the hemolytic process during the intrauterine stage, the amniotic fluid may be discolored, greenish-yellow.

I think it is important not to pay any attention to lack of visible jaundice at birth in making any statement regarding the severity or prognosis of the disease. The same holds true for anemia. It is extremely difficult to detect or exclude anemia on clinical grounds. The most reliable sign in our opinion for making a clinical diagnosis is enlargement of the spleen. Even in very mildly affected infants, it is often possible to palpate an

enlarged spleen, the only physical sign of the disease. The fact that there is a normal hemoglobin content in the cord blood does not mean that there has been no increased hemolysis but only that the infant's hematopoietic organs have been capable of maintaining equilibrium between destruction and production of red cells.

Not infrequently, however, there is not a single sign of the disease. The case just presented belongs to this group. How can the physician who suspects the disease on clinical or other grounds confirm this by laboratory tests? With the availability of anti-human-globulin serum, the laboratory diagnosis has become extremely simple. The direct Coombs test indicates whether the red cells of the infant are coated with antibody. A positive direct Coombs test is usually sufficient proof of the disease. A negative test, however, does not exclude erythroblastosis. The result might be a false negative, due to technical errors, or a true negative. The true negative Coombs test does not exclude the possibility of erythroblastosis due to immunization with A, B or antigens. Strangely enough, in such cases the direct Coombs test is usually negative. Other serologic tests are necessary to establish the diagnosis. In relation to the Coombs test it is worth while to know that, contrary to a common opinion, the strength of the reaction in this test has nothing to do with the severity of the disease or the prognosis.

After birth, the disease again runs a very variable course. It is better perhaps to keep in mind extensive physiologic alterations which occur after birth, and can activate the hemolytic process instead of assuming that there is a change in the basic pathophysiology of the disease. Due to changes of environment the typical symptoms of hemolysis, anemia, and jaundice begin to appear. After severance of the umbilical cord the infant must live his own existence and has no further connection with the maternal circulation. This means that he has to eliminate the excessive amounts of bilirubin and other pigments of hemoglobin catabolism all by himself. Depending on the degree of hemolysis he soon becomes jaundiced because he is not able to excrete sufficiently the pigments. His excretory liver function and the degree of hemolysis determine the degree of bilirubinemia.

In the case just presented, the infant's liver must have been able to handle the excessive amounts of bilirubin, because during his neonatal days no skin-jaundice was visible. Concerning the development of the anemia it is important to know that soon after birth red blood cell production is physiologically decreased, due to a considerable improvement of the oxygenation of the bone marrow. This means that without any change in the rate of hemolysis an anemia soon develops. Thus, an increase in the destruction of erythrocytes after birth is not necessary to explain the anemia and the jaundice, although on first sight this would seem to be the case.

Now some short remarks on the treatment. For those babies dying in utero or shortly thereafter, there still is not any treatment available. The only way to avoid such deaths would be to prevent hemolysis. ACTH and cortisone therapy are not able to prevent hemolysis during neonatal life. Nor do I think that there are methods available to interfere with the hemolytic process during the intrauterine stage.

Those babies born alive and surviving the dangers of the birth process itself can be treated very satisfactorily. When on clinical grounds the diagnosis can be made, i.e., if there are detectable signs of the disease present at birth, there should be no delay in doing an exchange transfusion. Exchange transfusion is the only rational treatment for the disease. Because this procedure is based upon prevention of further hemolysis, there should be no delay in its execution. Simple transfusions are irrational and are possibly not without harm. At the moment of birth many infants are in cardiac failure; increase of their already high venous pressure is contraindicated. The best way to treat these infants of the most severe, living group, is to bleed them first to lower the venous pressure and immediately following this to replace their blood with blood that can not be destroyed by the hemolyzing antibodies.

There is, however, a large group of newborns only slightly or not at all affected. In considering blood replacement in this group, it is important to keep two things in mind: First, what is the previous history; second, is the baby mature? If the previous history includes death from the disease or from kernicterus, in any siblings, there is a definite indication for exchange transfusion even if a positive Coombs test is the only positive sign. If the newborn is premature this is also a definite indication. The reason for this is that in these infants the excretory liver capacity is much decreased. Even without any increase in hemolysis they are not able to excrete rapidly the normal quantity of bilirubin from the physiologic breakdown of their red cells.

In an infant without these positive indications for exchange transfusions, the key to treatment is watchful expectancy. It is not necessary to decide within a short time whether to do an exchange. A blood replacement can safely be done at the age of three, four or five days. The degree of bilirubinemia is the most important guide.

If there is a rapid and severe jaundice in the first hours after birth we have already lost time. It is important for the physician and for the nurse in the nursery to observe a suspected case very closely for development of jaundice. A serum bilirubin determination is of much more value than serial hemoglobin determinations. From the laboratory standpoint, there might be a completely normal hemoglobin content of the capillary blood and a venous sample might show a definite anemia; in the first days of

life the difference between a peripheral and a venous sample for hemoglobin is sometimes greater than 6 grams. Moreover it is a potential anemia which needs treatment. The microdetermination of the serum bilirubin, as proposed by Diamond, could be an extremely helpful procedure in the deciding whether to do a blood replacement. In the neonatal period the babies with erythroblastosis die from kernicterus, not from anemia. As has been shown statistically by Diamond, there is a very close correlation between kernicterus and the degree of bilirubinemia. The jaundice and the serum bilirubin, therefore, are the best guides for treatment.

The case presented apparently did not show any jaundice during its hospitalization. This certainly is an instance where exchange transfusion was out of the question. This case belongs to the group from which we hear at an older age for the first time. The reason they see the doctor is their increasing anemia. They show the first symptoms of the disease after the first week of age. The treatment is very simple and consists of giving small transfusions of packed red cells of a suitable blood group. We should, however, not try to raise their hemoglobin content to a level considered normal for their age. It is better to keep the hemoglobin on the lower side and maintain an anoxic stimulus to the bone marrow, because in this way, the duration of the disease is shortened. The more red blood cells of the infant's own blood group are produced, the sooner are the antibodies bound and eliminated. The ultimate and complete antibody destruction is accelerated. I wouldn't be surprised if this child is admitted again shortly, because there may still be antibodies in her circulation. If so, we can be sure that she will develop an anemia again; the only way to treat her will again be to transfuse.



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